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# **Post-exposure Prophylaxis with Hepatitis A Vaccine**

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**ACIP Meeting, June 2007**

**Ryan Novak**

# Hepatitis A Vaccine Postexposure Today's Topics

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- **Summary of February ACIP meeting**
- **Summary of work group activity**
- **Context and potential policy implications**
- **Draft PEP recommendation**
- **Draft travel recommendation**
- **VFC vote (if needed)**

# **Hepatitis A Postexposure Prophylaxis**

## **Current ACIP Recommendation**

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- **A single dose of immune globulin as soon as possible [within 2 weeks of exposure]**
  - **If hepatitis A vaccine also is recommended, can be administered simultaneously with IG**
- **“Results of an appropriately designed clinical trial comparing the postexposure efficacy of vaccine with IG are needed to determine if hepatitis A vaccine without IG can be recommended”.**

# Summary of February ACIP Meeting

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- **Results of a clinical trial comparing efficacy of hepatitis A vaccine and immune globulin after exposure**
- **Discussion of these data and policy implication of using hepatitis A vaccine alone postexposure**
- **Vote tabled until June ACIP meeting pending a working group analysis**

# Summary of Work Group Meetings

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- **Availability of data**
  - Ages 2-18 and 19-40 years
  - Ages older than 40 years
  - Patients with chronic liver disease and other underlying medical conditions
- **Review of patient characteristics associated with more severe outcomes**
- **Response to vaccine**
- **Risk of transmission in common scenarios in which postexposure prophylaxis is given in the United States**
- **Experience from other countries**
  - UK, Canada

# **Rationale for Proposed Recommendations**

# Hepatitis A Vaccine Postexposure Rationale

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- **Benefits of vaccine**
  - Long term protection
  - Ease of administration
  - Acceptability
  - Availability
    - Single US manufacturer of IG
- **Cost similar to IG**
- **Brings U.S. practice in line with many other countries that provide postexposure prophylaxis**

# Randomized Clinical Noninferiority Hepatitis A Vaccine Postexposure Trial – Almaty, Kazakhstan

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- Enrolled 4,524 household or daycare contacts (aged 2-40 years)
- Exposed to index case within 2 weeks after index case symptom onset
- No history of hepatitis A or receipt of hepatitis A vaccine or IG (within past 6 months), chronic liver disease, or contraindications to vaccine or IG
- 1:1 randomization *within* households or daycare center classrooms to receive vaccine (VAQTA) or IG (Massachusetts Biological Laboratories) within 2 weeks after index case symptom onset
- Primary outcome – clinical hepatitis A
  - Positive for IgM anti-HAV
  - A serum ALT level at least 2x the upper limit of normal
  - Symptoms consistent with viral hepatitis

# Randomized Clinical Noninferiority Trial

## Summary of Findings

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- Hepatitis A vaccine efficacy was similar to that of IG (noninferiority criteria was met)
  - Assuming 90% IG efficacy, point estimate of vaccine efficacy is 86%; 95% CI upper bound is 76%
  - Assuming 85% IG efficacy, point estimate of vaccine efficacy is 80%; 95% CI upper bound is 64%
- Risk of hepatitis A among vaccine recipients was never > 1.5% greater than among IG recipients
- No evidence that vaccine given in second week postexposure resulted in lower clinical protection
- Evidence that IG might attenuate clinical illness

# Risks of Developing Hepatitis A Among Vaccine and IG Recipients by Age (ITTs): Children v. Adults

Clinical endpoints	Risks		Relative Risk
	Vaccine (n=740)  (risk)	IG (n=674)  No. (risk)	RR (95% CI UB)
Primary endpoint	26 (3.5%)	18 (2.7%)	1.32 (2.30)
2 to 18 years	21/628 (3.3%)	13/535 (2.4%)	1.38 (2.65)
19 to 40 years	5/112 (4.5%)	5/139 (3.6%)	1.24 (4.33)
All suspected hepatitis A cases	35 (4.7%)	27 (4.0%)	1.18 (1.87)
2 to 18 years	28/628 (4.5%)	20/535 (3.7%)	1.19 (2.03)
19 to 40 years	7/112 (6.3%)	7/139 (5.0%)	1.24 (3.47)

# Implications of Postexposure Study Findings: Children and Adults

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- **Children aged 2—18 years**
  - Data support vaccine equivalency to IG
- **Adults aged 19—40 years**
  - Wider confidence intervals around point estimates of relative risk
    - Small sample size in this age category
  - No significant difference in crude estimate of average ALT levels
  - Data supported vaccine equivalency to IG
- **For healthy persons age  $\geq 12$  months – 40 years, hepatitis A vaccine at the age appropriate dose is preferred to IG because of vaccine's advantages, including long term protection and ease of administration.**

# **Populations not Studied in Clinical Trials: Children aged 12 – 24 months**

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- **Almaty trial only enrolled children 24 months and older because vaccine not yet licensed down to 12 months in the U.S.**
- **No interference from maternal antibody – passive antibody gone by 12 months\***
- **Immunogenicity at 12 months similar to 24 months\***
- **Vaccine licensed from one year in every country**
- **Current vaccine recommendation includes this age group**

\* Source: Bell BP et. al., *Pediatr Infect Dis J* 2007.

# **Populations Not Studied in Clinical Trials: Older Adults**

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- **Almaty, Kazakhstan clinical trial**
  - Essentially all adults >40 are immune to hepatitis A
  - Persons aged >40 excluded from study population
- **No additional data available to support preference for vaccine**
- **Risk of severe complications increases with increasing age**

# Clinical Characteristics of Patients with Acute Hepatitis A, by Age Group – U.S., 2005

	<5			5-14			15-39			40-59			60+		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
Died from Hepatitis	0	107	0.0	0	358	0.0	4	744	0.5	3	457	0.7	5	278	1.8
Hospitalized For Hepatitis	23	117	19.7	84	362	23.2	224	686	32.7	155	440	35.2	144	308	46.8

Source: MMWR, vol. 56, No. SS-3

# Populations not Studied in Clinical Trials: Older Adults

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- No data about vaccine performance postexposure in this age group
- Risk of severe hepatitis A increases with increasing age
- For persons > 40 years, IG is preferred because of the absence of information regarding vaccine performance and the more severe manifestations of hepatitis A in this age group. Vaccine can be used if IG cannot be obtained.

# **Populations not Studied in Clinical Trials: Patients with Chronic Liver Disease and Other Medical Conditions**

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- **Chronic liver disease and other chronic medical conditions**
  - **Known to have poorer response to vaccine pre-exposure**
  - **Chronic liver disease patients have more severe disease outcomes**

# Response to One Dose of Hepatitis A Vaccines in Selected Populations

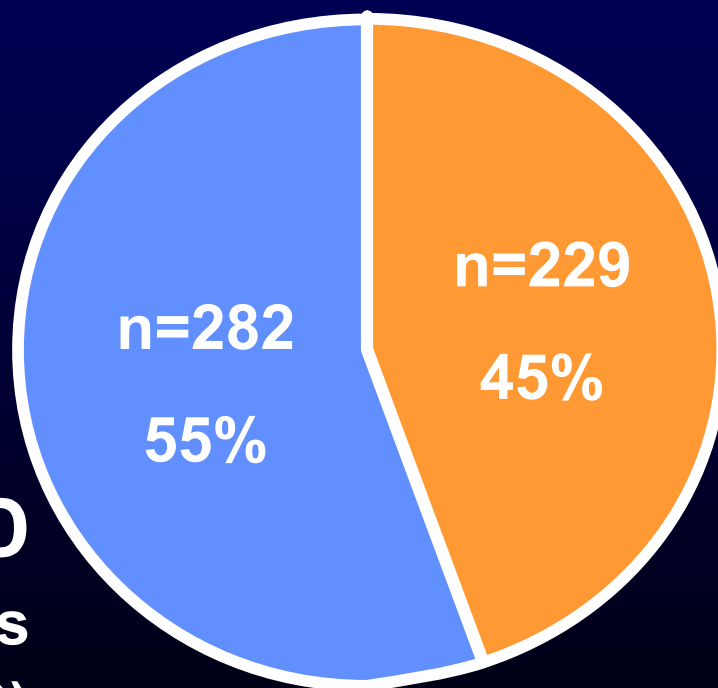
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Study Population	# Studies	% positive (4 weeks)	Comment
HIV infected	3	10%-78%	Higher with higher CD4 cell count
Chronic liver disease	3	63%-93%	Lower than controls; lowest in decompensated cirrhotics
Liver or Kidney Transplantation	3	0%-41%	

# Chronic Liver Disease Among Hepatitis A Deaths – U.S. 1999-2004

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Hepatitis A Deaths (n=511)



**CLD**

Median age – 55 years  
(Range: <1-95)

**non-CLD**

Median age – 69 years  
(range: <1-99)

# **Populations not Studied in Clinical Trials: Patients with Chronic Liver Disease and Other Medical Conditions**

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- IG should be used for children age < 12 months, immunocompromised persons, persons who have been diagnosed with chronic liver disease, and persons for whom vaccine is contraindicated.

# **Risk of Transmission of Hepatitis A Virus: Common Scenarios in which Postexposure Prophylaxis is Given in the United States**

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- **Decisions to use vaccine or IG should take into account risk of hepatitis A virus transmission from the exposure**
- **Household and other close personal contact**
  - **Secondary attack rates of 15-30%**
  - **Higher rates of transmission occurring from infected young children than from adolescents and adults**

# **Risk of Transmission of Hepatitis A Virus: Common Scenarios in which Postexposure Prophylaxis is Given in the United States**

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- **Exposure to infected foodhandler**
  - 3-7% of reported cases are foodhandlers
  - ~5% worked while infectious, pose transmission risk\*
    - Majority of foodhandlers do not transmit HAV to patrons
    - Attack rates generally low
  - Average ~350 IG doses per episode\*
    - Broad range – several thousand doses not uncommon
- **...decisions to use vaccine or IG should take into account patient characteristics associated with more severe manifestations of hepatitis A ... Additionally, the magnitude of the risk of HAV transmission from the exposure should be considered.**

# Hepatitis A Vaccine Postexposure Recommendations from Selected Countries

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- **Canada (2000)**
  - Vaccine without IG is preferred method of post-exposure prophylaxis
  - IG for infants and immunocompromised
  - One report of possible breakthrough infections found to be a transmission chain involving outbreaks in several child day care settings
- **UK (2001)**
  - Vaccine when exposure < 7 days
  - IG when exposure > 7 days or age > 50 years, cirrhosis, chronic HBV or HCV infection

# Hepatitis A Vaccine or Immune Globulin Postexposure Summary

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- **Vaccine offers a number of advantages over IG**
  - Flexibility to use vaccine in some circumstances would be beneficial
- **Available data suggest vaccine is efficacious postexposure, but not all populations were studied**
- **Suboptimal response to vaccine among patients with CLD or other chronic medical conditions**
- **Additional data not likely to be forthcoming**
- **Need to balance practical public health implementation considerations against limitations of available information**



# Hepatitis A Vaccine or Immune Globulin Postexposure Additional Materials

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- Current postexposure prophylaxis ACIP statement
- Proposed postexposure prophylaxis (PEP) language
  - Common settings in which PEP given in the U.S.
    - Close personal contact
    - Child Care Centers
    - Common-source exposures
    - Schools, hospitals, and work settings
    - **Substituted “IG or hepatitis A vaccine” for IG**
- Proposed new travel recommendations for timing of pre-exposure vaccination dose

# Hepatitis A Vaccine Postexposure Draft Recommendation, Paragraph 1

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Persons who recently have been exposed to HAV and who previously have not received hepatitis A vaccine should be administered one dose of single antigen hepatitis A vaccine or IG (0.02 mL/kg) as soon as possible. Information about the relative efficacy of vaccine compared to IG postexposure is limited, and no data are available in persons aged > 40 years or those with underlying medical conditions. Therefore, decisions to use vaccine or IG should take into account patient characteristics associated with more severe manifestations of hepatitis A, including older age and chronic liver disease.

# Hepatitis A Vaccine Postexposure Draft Recommendation, Paragraph 2

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- For healthy persons age  $\geq 12$  months – 40 years, hepatitis A vaccine at the age appropriate dose is preferred to IG because of vaccine's advantages, including long term protection and ease of administration.
- For persons  $> 40$  years, IG is preferred because of the absence of information regarding vaccine performance and the more severe manifestations of hepatitis A in this age group. Vaccine can be used if IG cannot be obtained. The magnitude of the risk of HAV transmission from the exposure should be considered in decisions to use vaccine or IG.
- IG should be used for children age  $< 12$  months, immunocompromised persons, persons who have been diagnosed with chronic liver disease, and persons for whom vaccine is contraindicated.

# Hepatitis A Vaccine Postexposure Draft Recommendation, Paragraph 3

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Persons administered IG for whom hepatitis A vaccine is also recommended should receive a dose of vaccine simultaneously with IG. For persons who receive vaccine, the second dose should be administered according to the licensed schedule to complete the series. The efficacy of IG or vaccine when administered > 2 weeks after exposure has not been established.



# Current ACIP Recommendations for Pre-Exposure Protection Against Hepatitis A -- Travelers

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- **Vaccine only**
  - Travelers departing >4 weeks
- **Vaccine (IG may be given for optimal protection)**
  - Travelers departing <4 weeks
- **IG only**
  - Aged <12 months
  - Allergic to vaccine component
  - Elect not to receive vaccine

# **Rationale for Revisions of Hepatitis A Vaccine Recommendations for At-risk Travelers**

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- **Almaty study findings and the new post-exposure recommendations**
- **Relevant to preexposure vaccine use among at-risk travelers**
  - **Vaccine administered anytime prior to departure should adequately protect most travelers**
  - **May not be generalizable to all populations**

# Hepatitis A Vaccine Travel

## Draft Recommendation, Paragraph 1

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The first dose of hepatitis A vaccine should be administered as soon as travel is considered. Based on limited data showing equivalent postexposure efficacy of IG and vaccine among healthy persons aged  $\leq 40$  years, one dose of single antigen hepatitis A vaccine administered at any time before departure may provide adequate protection for most healthy individuals. However, no data are available for other populations or vaccine formulations (e.g. TWINRIX). For optimal protection, older adults, immunocompromised persons, and persons with chronic liver disease or other chronic medical conditions traveling to an area less than 2 weeks after the initial dose and where risk of transmission is high may also be administered IG (0.02 mL/kg), but at a different anatomic injection site. Completion of the vaccine series according to the licensed schedule is necessary for long-term protection.

# Hepatitis A Vaccine Travel Draft Recommendation, Paragraph 2

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Travelers who elect not to receive vaccine, are < 12 months of age, or allergic to a vaccine component should receive a single dose of IG, which provides effective protection against hepatitis A for up to 3 months. Travelers whose travel period is >2 months should be administered IG at 0.06 mL/kg; administration must be repeated if the travel period is >5 months (see full statement for licensed vaccination schedule and recommended dose of IG and vaccine; <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5507a1.htm>).

